A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:06 p.m.)

DR. SUGAR: Okay, if there's no objection, I'd like to proceed with the additional comments from the sponsor. They've asked for a few more minutes than the 5 minutes on the program and I think that that's reasonable. So go ahead.

DR. McDONALD: Thank you, Dr. Sugar. We would like to specifically address Dr. Berman's questions to the Panel.

Question 1 relates to concerns regarding induced cylinder. As you have seen both in our presentation and presented by Dr. Berman, induced cylinder was observed in a fairly high proportion of eyes at the 1-month examination. However, the frequency and magnitude decreased significantly over time and was well below the current FDA limit of less than 5 percent. From 6 months, the proportion of eyes with induced cylinder of greater than 2D also meets the more stringent proposed limit of less than 1 percent.

This graph shows UCVA over time in eyes with greater than 1D induced cylinder at 1 month, consistent with the resolution of induced cylinder over time, uncorrected acuity improved substantially

from 1 through 12 months.

Induced cylinder had no affect on BSCVA, with all eyes at 20/32 or better at 12 months. The magnitude of effect of induced cylinder greater than 1.00 diopter on UCVA was on average one line less improvement, irrespective of whether the analysis was performed using absolute magnitude of induced cylinder or vector analysis. Similar results were obtained when considering induced cylinder greater than or equal to 1.00 diopter. There was no effect on UCVA in eyes with manifest cylinder greater than 0.75 D with an axis shift of 30 degrees or more.

In summary, we've shown that induced cylinder meets the current FDA limit and decreases significantly over time, resolving in a large proportion of the eyes. This resolution of induced cylinder was not attributable to regression of the spherical correction. The presence of induced cylinder greater than 1D and greater than or equal to 1D was associated with a difference of approximately one line of improvement in UCVA. UCVA improved over time as induced cylinder resolved, and the difference in UCVA translated into a lower proportion of eyes with UCVA of 20/20 or better. Induced cylinder had no effect on best corrected visual acuity irrespective of

the analysis performed.

Question 2 relates to whether a 12-month follow-up is adequate to support safety and effectiveness. Because the 9-month population of 376 eyes presented in our PMA represents 94 percent of all eyes, and the 12-month population of 203 eyes represents 51 percent of all eyes treated, but 97 percent of the eyes eligible for examination, we believe the available data provide reasonable assurance of safety and effectiveness. Updated 12-month data and the available 24-month data have been submitted to the FDA for review and the results for key parameters of safety and effectiveness are consistent with the data reviewed by the Panel. Refractec is more than willing to update all labeling information to reflect the additional data.

Question 3 asks whether the refractive correction effected by CK justifies the risks. Predictability of the CK procedure is presented here graphically to display the proportion of eyes that were under-corrected and over-corrected. The proportion of eyes initially over-corrected decreased substantially after one month and under-correction was limited to a small number of eyes throughout the course of the study.

The stability target identified in FDA guidance of change in MRSE within .50 or 1.00 diopter was achieved at both the 6 to 9 and 9 to 12 month intervals. Using a paired analysis between months 6 and 9, the mean change per month in the manifest or fraction was 0.03D while mean change was 0.04D between 9 and 12 months. However, these data did not achieve the remaining two FDA stability criteria of decrease in mean change over time to an asymptote and the confidence interval encompassing zero.

As shown in this graph, there was a very close match between the manifest and cycloplegic refractions over the course of the study. This graph also shows the relatively small initial over-correction following the CK procedure, particularly in comparison to other refractive procedures for hyperopia correction. This over-correction has generally been acceptable to patients and that it is mild and temporary. Hyperopia is reached at approximately 6 months and there is less than a .25 diopter of change between 6 and 12 months.

FDA poses the very fundamental question of whether the potential risks of the CK procedure are justified in light of the rate of change in MRSE over time and the proportion of under-corrections and

over-corrections. The first point to be made in response to this question is that hyperopic patients seeking correction of their distance vision in this study experienced a significant improvement in UCVA. Fifty percent of all eyes had UCVA of 20/20 or better and over 90 percent had UCVA of 20/40 or better. This was accomplished with no serious adverse events or complications, no incursion into the visual axis and no removal of tissue. Additionally, 95 percent of patients felt that their quality of vision was improved.

We have shown you data establishing the rate of change in MSRE to be very small, less than a .50 diopter per year, based on the mean change from 9 to 12 months. The concerns regarding under-corrections and over-corrections are valid, but are also pertinent to all refractive surgery procedures for correction of hyperopia. As with all corneal steepening procedures, there is an initial over-correction following CK, but those are relatively small and resolves early. Only a small number of eyes were under-corrected over the course of the study.

To speak to the issue of whether the potential risks of the CK procedure are justified, we ask you to consider the risks associated with Lasik as

described in the FDA's website for patients considering Lasik surgery. These risks include under treatment or over treatment, loss of vision that cannot be corrected with spectacles or contact lenses and loss of effect over time. As a refractive surgeon, I can also tell you that I continue to have concerns with regard to Lasik complications such as "Sands of the Sahara" or DLK, micro and macro striae, aborted flaps, lost flaps and of course, the most serious of Lasik complications, entry into the anterior chamber with the microkeratome blade.

We believe that CK offers patients considering vision correction a viable alternative to Lasik and other modalities for the correction of hyperopia with a comparable risk to benefit ratio.

Question 4 relates to the visual symptoms reported in our study. The increase in symptoms reported as moderate and marked was limited to 5 to 7 percent, thus just exceeding the threshold of 5 percent defined as clinically relevant. More importantly, the increase in marked symptoms reported at 6 months largely resolved at 9 and 12 months. Finally, there was no significant increase in very severe symptoms at any time during the study.

Question 5 asks whether the safety and

efficacy data support approval of CK for the indication proposed. To summarize the effectiveness data, you have seen that the results for UCVA and accuracy of the refractive outcome exceeded FDA targets for these parameters. Stability was not achieved, but the average change per month in MSRE was small, annualized to less than a .50 diopter per year. Ninety-four percent of the intended correction remains at 12 months and 80 percent of patients reported being satisfied or very satisfied with the results of the procedure.

All FDA limits for safety were met in the study population. Only 1 percent or less of eyes lost greater than 2 lines of BSCVA and no eyes had best corrected acuity worse than 20/40 at 6, 9 or 12 months post-op. Finally, the incidence of induced cylinder was considerably below the current limit in FDA guidance.

To summarize, we believe that the results of the clinical trial of CK serve to establish the safety and effectiveness of this procedure and also serve to support the proposed indication for use.

Question 6 speaks to recommendations for labeling. While we welcome further recommendations from the Panel and from the FDA for labeling, we have

proposed for your consideration labeling information that serves to address concerns that should be communicated to physicians and patients considering the CK procedure. Specifically, we suggest that loss of effect over time be communicated by reporting the proportion of intended correction retained at one year in this study population, while noting that loss of effect may continue beyond one year.

With regard to over-correction, it should be communicated that patients may experience an initial over-correction and that this may affect distance vision such that spectacles are required for driving. Next, although we have not specifically discussed this during our presentations, we have already included information in the labeling, stating that accuracy of the intended correction was slightly lower for eyes in the higher dioptric range. We will also address the lower proportion of eyes with UCVA 20/20 or better in the higher dioptric range.

With regard to induced cylinder, we propose communicating that induced cylinder greater than 1D was associated with less improvement in UCVA at the 20/20 and 20/25 levels and that achievement of UCVA of 20/40 or better was somewhat delayed. Information on symptoms has already been included in

the labeling in our PMA and can be revised as determined appropriate by Panel and the FDA.

Finally, as suggested in the Panel review, we will add to our labeling a statement indicating that no data are available on re-treatment.

This concludes our presentation. We would like to thank the Panel Members, particularly the primary reviewers and the FDA personnel for the significant time and effort invested in their thorough and insightful review of the clinical data in our PMA. We also thank you for your consideration of the CK procedure as a safe and effective refractive surgery option for hyperopic patients.

DR. SUGAR: Thank you. We will, I think, reserve the option of asking questions as they arise from you, but it's fine to go back to the audience.

Now we proceed with the committee deliberations and begin with the primary Panel reviewers. First will be Dr. Arthur Bradley.

DR. BRADLEY: Arthur Bradley. A couple of things to remind everybody here, that I'm not a clinician and the original review of this PMA was done back in August and I had to re-frequent myself with this document a few days ago and some of my comments relate to some of the frustrations experienced at that

time.

I want to go through several points here. First, an issue about presentation of the data. This really applies to the sponsor and also to the FDA. I'm trying to think of more effective ways of communicating complicated data sets because I found the current document really quite difficult to manage. I'm then going to concentrate on what I call the main effect, as the change in manifest refractive spherical equivalent. The issue there, of course, is over or under correction and much has been said already about stability. I'm going to add a few comments about stability and we then get into this issue of induced astigmatism and in particular, I'm going to comment on how this might be presented in a more easy to understand way.

I'm then going to talk about interactions with any procedure. We always look for significant interactions and I found that very difficult to extract from the data set and finally some issues about patient information which, in many ways, don't stem from my expertise as a scientist, but my position as a potential customer.

Let's go through one by one. Presentation of the data. Indeed, a complicated data set, but

hundreds of tables, I'm not really sure exactly how many tables I looked through but my mind was spinning. I think in the last document I was at Table 109.2, entitled "Induced Cylinder Residual Astigmatic Error at Stability time Point. All Eyes Treated at Month 12." Really, 109 data tables makes me wonder if this is just an inefficient way to present the data. There might be better ways to do it. And certainly as a teacher of graduate students, I have to communicate all the time that numerical effectively communicated in a graphical format -- tables often do a very poor job of communicating data.

Still, sometimes the main data are never presented or are hidden or are inadequately.

(Laughter.)

Here's a good example of that. Look at that.

(Laughter.)

I don't know what that was all about. I think the system is reacting to having a McIntosh attached to it, basically.

What have we got here? The sponsor has presented the data in terms of -- yeah, so this last comment really is I think the way the data have been presented. I think the sponsor has done a fabulous

job, by the way of communicating to us what proportion of the data meets certain criteria and the criteria are really, have been dictated by the FDA, a certain number of people have to have uncorrected VA of a certain level. Residual refractive error must be less than a certain percentage and have more than 1.00 diopter, etcetera. And in the end, that's how the data have been communicated and in the teaching environment in which I work, the one thing that I continually have to remind my students of is that before I know the statistics on a data set, I really want to know the data set. In the end, I think that was what really bothered me and gave me so much trouble with this particular proposal and that was the data were perhaps not presented. More the analysis of the data was presented. So if I had an opportunity here to encourage the FDA and the sponsor or future sponsors, is to first present the data and then we'll have a look at the analysis and if we could see the data directly, I think we would learn quite a bit more.

Here's just an example. The most important thing really for us to know is the issue of how much did the refractive error change. And I looked really hard and I think as my son could tell

you, I'm not the best searcher of things in the world, but I couldn't find a graph that showed the mean spherical equivalent refractive error for this patient set and we've seen it this morning, by the way. A couple of presenters from the sponsor presented this graph. But it isn't in the report and that would have helped tremendously. It turns out the data are shown on Table 69 at page 154 of Volume II, but only after amendment 11, dated September 7th, did the pre and post MRSE appear together as Table 1D.1. And as far as I could tell the original narrative didn't even provide that information and it seems to me that is the main reason for doing the procedure. Surely, this should have had a very prominent position in the report.

Well, I did my own analysis and actually graphed the data and this is the graph we've already seen. It's the pre-1 month, post 3-months, 6 months, 9 months, 12 months and we've got the manifest and the cycloplegic refraction there and you see, as the sponsor has shown us this morning that these are really essentially identical and a couple of things to point out here. This is the myopic overshoot we're a bit worried about. At month 1, it's still there at month 3. The mean is about plano at month 6 and

drifting slightly into hyperopia by 12 months and that's exactly the result we've seen already.

And these are the average data, so on average we've got over-correction early on, under correction later on, but this is for the whole sample.

From the most recent data set, I took out the standard deviation data and simply added those. That should say one standard deviation here. And there's the mean again that I've just shown you and that's one standard deviation in one direction, two standard deviations. One standard deviation, two deviations. And there are a couple of important things to note here, particularly in that early time period of one month. Although the mean is only about .50 diopter here, once we get out at two standard deviations and really that encompasses the whole distribution of plus or minus 2 standard deviations, some people are hovering out there at 2.00 diopters of myopia and these are the ones that worry me the most, these particular patients.

Something that's quite hard to see in this graph, but I'll show you in the next graph and something that you should think about is notice the pre-op range of data. That's the data here we'll call time zero. Time zero here. It's ranging from about

+2.8 down here to about +.3 or .4, that's the range. Notice that the range doesn't get any smaller. It turns out the standard deviations actually climb as we -- after the procedure. So the post-op standard deviations are actually larger than the pre-op. I've got a little note down here, expectation. First of all, we expect the refractive error to converge towards emmetropia after appropriate levels of CK, the idea being is that CK can come, you can have 32, 8, 16, 24 different amounts of the procedure done, all designed to accommodate the pre-op refractive error and target everybody towards emmetropia. So that's the goal of having different levels of CK.

We know the mean is myopia and as I said, it's very significant for some eyes, but here's the -- unusual result. The refractive error distribution is wider after the procedure. Now how could that happen because everybody should be targeted to the same results, starting from different locations and the fact that the distribution after the procedure is wider than it is before makes one realize that this is not a highly controlled procedure in which irrespective of starting point we can converge the distribution down on to zero, on to plano. In fact, the distribution spreads, a larger distribution after

than before the procedure, indicating significant course of variability in the procedure.

This is just a graph plotting that. Standard deviation is a function of time, zero being pre-op, standard deviation .6 diopter. It climbed 60 percent up to that point, 95 percent. Thing to remember, if you gave every eye the same CK procedure, identical, you would expect the standard deviation to remain constant, but by selecting the appropriate levels of CK we expect the post-op standard deviation to be significantly lower. In fact, it's higher. We really have no explanation for that, except that the procedure is introducing a huge amount of variability and maybe the sponsor could comment on that at some point.

Next issue on my list. Stability. Well, we've seen lots of talk about it and we've seen a variety of numbers thrown around but most striking to me is the commentary and the commentary is this. We've got data at 1 month, 3 months, 6 months, 9 months and 12 months. And that's exactly the graph I've shown you before and all I've done is extrapolated the 9 to 12 month data on out. So these are all from -- that's real data. This is extrapolation, extrapolation. Just to remind

everybody, another word for extrapolation is speculation. We don't have the data here, here and here, but I'm just extrapolating the last two data points on out.

A couple of things to note. Indeed, the change from here to here is quite small and we've heard the sponsor tell us it's very small, insignificant, tiny. In fact, in the original submission this was called stable. So all I did was extrapolate that. I remember these are not real data here. This is all me speculating, based upon a linear extrapolation of the data between 9 and 12 months, the point being that as the sponsor in its amendment 11 or submission 11 gave us this result as a percentage of the targeted refractive change and it was something like 90 percent so there had been a bit of regression, got down to about 90 percent. The important point to note is you continue that out at four years, the percentage of the refractive error change will be zero. Like I said, these are not real data. This is just me making it up. It would be nice to have these data and if there was some indication of stability here, that is, this change asymptoted out to a flat line, then I think extrapolating that out will be in this direction and indeed, we would be concluding that

there was not significant regression, but because the last data set had this slope, if we are extrapolate which I never liked to do, but I'm just doing -- my McIntosh will come back.

(Pause.)

Okay, so any way that's just a little story about stability and I don't quite know what to say about that. There is no evidence of stability and you know the alarming thing is that would keep on and we'd have zero correction, but like I say I don't know that's going to happen.

Astigmatism. Does the procedure induce significant amounts of astigmatism? Now, astigmatism is an inherently two dimensional variable. We all know that, axis and magnitude. But the presentation always reduces that down to a one dimensional number. And it turns out when you do that you end up with some problems and they can be misleading and I'm quite familiar with astigmatism data sets and I really in the end was struggling to understand what had actually happened with induced astigmatism. For example, did the procedure introduce random astigmatism, was it consistent? How did the induced astigmatism vary with clinician and number of treatment spots, etcetera? These are all interesting questions I would have liked

to have seen answers to, but I didn't get them.

This is really by way of tutorial. I apologize for those of you who know this. It's me as a teacher coming in here. This is the one way we typically present astigmatic data. It's called vector analysis in the proposal and in some of the reviews and it's worth making a couple of points about it so we, in future, maybe could use this as a standard.

This is a little graph and in the graph it's a two dimensional graph, as you can see, horizontal, vertical axes. I've called this J0 which is sort of vertical horizontal astigmatism, J_{45} which is oblique astigmatism. Plus J0 is with the rule, -J0 is against the rule and this over here is one type of oblique astigmatism and this is the opposite oblique astigmatism. I've put three sets of data on here. One, two and three. These are three different eyes. The yellow circle is the astigmatism pre-treatment, pre-CK.

Now again this is all hypothetical, just to make a point. If the procedure introduced an astigmatism and that was a procedurally introduced astigmatism so we've talked about induce astigmatism, let's say this is it and it's the same for every eye. What you could imagine could happen with a stable

procedure. Then that would transfer this data point to there. This one to there. This one to there. It would be a constant effect here. That is a vector change from here to here.

Well, let's look at what happens as a result. Let's take Case No. 1, a certain amount of astigmatism. That was that black line here. We could describe that as its vector. It changes to this one. So clearly, there's a change in axis and there's a small change in magnitude. Well, let's take Case 2. This is the astigmatism to start with, you add it, you get this. There is no change in axis at all, none at all, but a large change in magnitude. Let's take Case No. 3. Starts off with this astigmatism. We add the procedural astigmatism and end up with this. The actual magnitude is exactly the same as what we started with, but a very large axis change, in this case -- plotted here it's 180, but it ends up being a 90 degree axis change. So you can see, depending on where you start a constant procedurally induced astigmatism produces quite different results. Sometimes you get a change in axis, sometimes you get a change in power, sometimes you get both. Presenting just one of those dimensions alone does not allow us to understand what really happened. It's very

important with two dimensional data that you present both dimensions. Otherwise, we can misinterpret it.

Is this academically interesting, but clinically irrelevant? Good question to ask, especially when I'm talking, but let me give you an example. Let's imagine this really is what happened. Again, this is all just speculation, just an example, but imagine you knew that this patient had this amount of astigmatism and you knew the procedure did this. The residual astigmatism in this case is going to be much greater than it was at the start. Whereas for this patient, you know that the final astigmatism is going to be basically the same as it was when it was started, just a different axis. So this patient might be discouraged from having the procedure. That would be one direct clinical application of this knowledge. But without this knowledge, you can't make that recommendation to a patient. So it's very important to present the data in a complete way.

A couple of things to be thinking about, astigmatism can be induced by two very obvious things. Any meridional anisotropy in the procedure. This is a hand-held device. This is an eye. The eye is moving, the angle at which you enter the needle into the cornea can vary. Clearly, there's a lot of

opportunity for this and maybe that is the reason for some of the results we see.

The other one is that the misalignment of the procedure axis from the visual axis and really it's the foveal line of sight. There are a few details that I would have liked to have seen in the presentation that we didn't learn about how this procedure axis, that is, the little ring that is inserted, that is painted out of the cornea is lined up with the eye. Is it really lined up on the foveal line of sight? How accurate is that misalignment of that as the people who are involved in laser refractive surgery know will induce astigmatism. So both of these can induce astigmatism. It would be nice to know which of these is actually involved, but I couldn't find any data that examined the root cause of the induced astigmatism and because the astigmatic were presented in a one dimensional way, I couldn't get a handle on what was going on.

Interactions. With refractive surgery there are always -- we're always very concerned about the procedure, how the procedure interacts with other parameters in the patient. For example, how does accuracy vary with pre-CK RX. How does induced astigmatism vary with pre-CK astigmatism? How does

post-CK BSCVA vary with pre-CK VA, etcetera, etcetera. I mean there are lots of interactions we'd like to know about. And there is a very effective graphic tool for identifying and visualizing such interactions. We call it the scattergram and I would have loved to have seen some of these scattergrams, but again, I say no graphs, but I can't recall seeing a graph and certainly not these scattergrams. Again, to get a handle on what the actual data were, not whether they met the FDA criteria, it would have been very helpful to see these and I just show again a hypothetical example here. If this is pre-procedure, MRSE and this is post-procedure MRSE and here's a little scattergraph of us, so we're plotting one against the other. This graph is a very familiar territory for us. We know if the data fall along the Y equals X line, CK has no effect. If the data fall along the post-refractive area equals zero, CK is perfect. If the data fall up here, we've got under-correction. If it falls down here we've got over-correction. We would have known this right away by looking at that graph. But we don't have that graph and I found that difficult to extract and that's just one example, but I could list tons of these.

Final point, again, this is not really me

speaking as a scientist, but as a potential patient, I really feel very strongly about this, the informed consent issue and having dealt with complicated optical effects and trying to communicate those to patients I realize that this is not an easy thing to do. I just pull out a couple of things. If I recall in the patient document there was some effort to make sure that the patient knew that they weren't going to have a laser irradiating their eye which is, of course, a very important thing for the patient to know and patients are quite concerned about lasers, justifiably so. But it paints the current procedure in a very reassuring light and talks about "gentle heat". I wonder what "gentle heat" really meant anyway, but you know I think if you're going to bring up the alarm bells of lasers, then I think to be fair, maybe you should explain that a sharp needle is going to be inserted into their eye up to 32 times, just to give balance there and so the patient really can make a judgment call. Do I want a laser or do I want a needle? As opposed to a laser versus "gentle heat". That just didn't seem to me a very accurate way to prevent a procedure to a patient.

Finally, and I think the sponsor has just discussed this in their final presentation, they are

going to and I think it's essential, that the patient who undergoes this procedure has a very good indication of the likelihood, the magnitude and the consequences of the post-procedure myopia and astigmatism that they are going to experience. The myopia particularly concerns me because -- but I would really like that because I think patients who have been hyperopic all their life to be converted to a myope, even if it's for a short period of time, they need to know about that and they need to appreciate the consequences, particularly as the sponsor has now conceded with regard to driving and particularly driving at night.

Thank you.

DR. SUGAR: Thank you. The next reviewer is Michael Grimmett.

(Pause.)

DR. BRADLEY: The system survived a McIntosh. Only just so.

DR. GRIMMETT: The following is not intended as a comprehensive substitute for my written comments dated August 11th, but I feel it necessary to highlight some of the notable features of the PMA, primarily as a foundation for my conclusions for the public record.

Regarding the study population, the original PMA only had 20 percent of eyes available at the 12-month interval, increasing to approximately 50 percent at the 12-month interval. There are no data submitted for the 24-month interval. Therefore, the study is submitted as incomplete.

As we've seen the accountability was quite good throughout the study, a greater than 97 percent at all time intervals.

First, I'll discuss issues related to safety. An important indicator of the safety of a refractive surgical procedure is no change in the best corrected visual acuity following a surgery. A month 6, approximately 5 percent lose greater than or equal to two lines of best corrected visual acuity, not an insignificant rate in my book. Presumably, the higher rates of best corrected visual acuity loss at the earlier time periods are due to corneal irregular astigmatism. Fortunately, the rates do decrease with time as we see in the graphical presentation that I hope meets Dr. Bradley's standards.

(Laughter.)

Looking over some subjective symptoms, pre-operatively, 26 percent of patients were complaining of mild, moderate or marked glare

symptoms, while post-op 38 percent complained of the same symptoms, an increase. Pre-op, 10 percent complained of mild, moderate or marked halo symptoms, while post-op, 35 percent complained of the same symptoms, a 3.5 fold increase. Pre-op, 10 percent complained of mild and marked double vision symptoms, while post-op 24 percent complained of the same symptoms, a 2.4 fold increase. Regarding fluctuation of vision, 16 percent pre-op complained of mild, moderate and marked fluctuation of vision symptoms, while post-op 40 percent complained of the same symptoms, a 2.5 fold increase.

Pre-op, 25 percent complained of mild, moderate or marked variation of vision symptoms, while post-op, 44 percent complained of the same symptoms, a 1.8 fold increase. Pre-op, 36 percent complained of mild, marked or very severe night time driving vision problems, while post-op, 42 percent complained of the same symptoms, an increase.

Hence, an increase in glare, halos, double vision, night driving problems, suggest the induction of higher order visual aberrations as a consequence of the procedure, that is, the induction of regular astigmatism, irregular astigmatism or the detrimental alteration of the normal corneal prolate asphericity

among others.

An increase in variation of vision and fluctuating vision may be the patient symptom and harbinger of refractive instability as we previously discussed. Appropriate labeling should include these symptom data.

A large percentage of patients, approximately 1 in 4 had the induction of greater than or equal to 1.00 diopter of astigmatism at the 6-month interval. Up to one third had the induction of greater than or equal to 1.00 diopter of cylinder at month 1. By month 12, there's an approximate two fold increase in the mean cylinder, .32 diopters pre-op to .68 diopters at month 12. If experiencing induced cylinder greater than or equal to 1.00 diopter, the uncorrected visual acuity declines as shown in Dr. Berman's slide 8 where 51 percent had 20/20 or better uncorrected vision of less than 1.00 diopter of cylinder and half of that or 24 percent had uncorrected visual acuity of greater than or equal to 1.00 diopter of cylinder.

Presumably, the induction of cylinder is related to asymmetric corneal shrinkage as a consequence of the procedure. Looking at greater than or equal to 1.50 diopters, approximately 1 in 15 had

that level of cylinder induction at the 6-month interval. Therefore, based on the cylinder data, appropriate labeling should include specific data regarding cylinder induction rates greater than or equal to 1.00, greater than or equal to 1.50 and greater than or equal to 2.00 diopters. Also include data regarding the loss of uncorrected visual acuity associated with the induced cylinder, and number three, it should delineate the instability of the induced cylinder with time.

Regarding cylinder axis, shifts in axis are somewhat random and generally spread across the range 0 to 90 degrees, a slight weighting towards shifts less than 15 degrees. Approximately 70 percent at Month 12 shift in axis greater than 10 degrees indicating there's a high probability that the direction of cylinder will be different post-op as compared to pre-op. Approximately 50 percent at month 12 shift greater than 30 degrees. Labeling should therefore indicate that the precise direction of induced cylinder is unpredictable and highly variable. The labeling should indicate that the axis shifts are more probable than not. Based on the data submitted, I was unable to determine if the astigmatism meridian is refractably stable in the long run.

Regarding the etiology of the induced cylinder, we can speculate that the high rate of induced cylinder may be due to a combination of factors. Number one, inaccurate spot placement. The technique requires a manual spot-by-spot placement on a corneal mark. It's improbable that any surgeon can place each spot with 100 percent precision in perfect symmetry. Also, if the optical zone markers is decentered, treatment asymmetry is a given.

Number two, asymmetric energy uptake, differing corneal thickness we can postulate may lead to asymmetric energy uptake and therefore may lead to asymmetric steepening, for example, the temporal cornea is thinner.

Number three, nonperpendicular needle tracks. Given the prolate asphericity of the cornea and the manual spot-by-spot placement technique, it's improbable that any surgeon can place each spot with 100 percent precision regarding perpendicularity.

Number four, a non-uniform needle dept, we can theorize that differing pressure by the surgeon with each spot placement and patient to patient tissue variability may indeed lead to differing treatment depths. All four of these factors may contribute to the induced cylinder seen with this technique.

Now on to some efficacy issues. As shown in Donder's table, accommodation at younger age is significant and can skew uncorrected visual acuity measurements toward better visual outcomes in a hyperopic population. Importantly, stratification by age in this study did not show a trend toward better uncorrected vision with the younger age group.

The Refractec data did disclose improved uncorrected visual acuity following the procedure as compared to pre-op levels. If we stratify this by dioptric group it appears reasonably matched at month 6, but the levels achieving 20/20 appear to decline by month 9 and month 12 disclosing lower rates of achieving these visions. Labeling should incorporate this fact.

For this procedure, as Dr. Bradley pointed out, emmetropia was intended in all cases. If the predictability of the procedure were good I would certainly expect the post-op standard deviation values to be lower than the pre-op standard deviation values and this is clearly not the case. Pre-op standard deviation of the mean post-op values are all higher. This would indicate that a wider spread of the data was created and suggests poor predictability of the procedure.

Looking at intended versus achieved correction. Fifty-eight percent achieved plus or minus half of intended while 91 percent achieved plus or minus 1 of intended. These exceed the relevant guidance document target values. I would simply point out that a patient with a low amount of hyperopia is likely interested in plus or minus a half. Certainly, a patient entering the study with 1.00 diopter of hyperopia, for example, is not going to care about a 4.00 diopter spread of predictability. I just want to make sure that labeling includes the range of the data for analysis.

If stratifying by the degree of hyperopia, there's declining predictability as the level of hyperopia increases as we can see here for both plus or minus a half and plus or minus 1. This is a find similar to many refractive procedures.

The proportion of under-corrections greater than +1.00 diopter is increased in the higher hyperopic group suggesting decreased efficacy with increasing levels of hyperopia. Appropriate labeling should delineate the declining procedure effectiveness as the pre-op level of hyperopia increases.

There was an approximate 1 in 10 rate of no or slight improvement in the quality of vision and

an approximate 1 in 10 rate of dissatisfaction. There were no differences found between differing hyperopic groups regarding satisfaction rates. Appropriate labeling should reflect these data.

Regarding stability, the proportion of over-corrections for the entire cohort decreases with time over the study periods suggesting refractive instability or loss of surgical effect as shown here graphically with time.

Additionally, as we've seen this data on a previous slide, the declining levels of induced cylinder with time also argues for refractive instability. It's reasonable to assume that shifting astigmatism may lead to complaints of fluctuating vision.

For a consistent cohort of eyes through month 12, the mean refraction does show a continuous rise as shown here, supporting refractive instability of loss of surgical effect. Over this particular study period, there was a .8 diopter loss from month 1 to month 12 or approximately 30 percent of the refractive effect was lost between month 1 and month 12. Of note, physiologic drift has been estimated to be less than .08 diopters per year and is therefore not likely to play a significant role in the hyperopic

drift seen in this particular study.

If analyzing the mean rate of change per year, there is a 1.00 diopter change per year if you utilize the data between 3 and 6 months. There's a .4 diopter change per year if looking at the data from 6 to 9 and a .48 diopter shift per year if looking at the data between 9 and 12 months. Importantly, the rate of shift is increasing at the latest study interval whose confidence interval does not include zero, indicating that a definitive stability point has not been reached. The stability of this procedure is therefore unproven.

As a historical perspective, the 10-year PERK Study results caused widespread concern regarding refractive instability when it disclosed a refractive shift of only .06 diopters per year, a rate of refractive change 8 times smaller than the current CK refractive shift from 9 to 12 months.

In support of refractive instability then we have the following features:

1. Increased variation of vision complaint.

2. Increased fluctuation of vision complaint.

3. Progressive declines in astigmatism

magnitudes.

4. Progressive declines in the percentage of over-corrections.

5. Progressive increase in the mean manifest refraction spherical equivalent in a continuous month to month refractive shift that increases at the latest time interval and whose confidence interval excludes zero.

Hence stability of this surgical procedure has not been established on the basis of these data. It is therefore mandatory that the study be completed with careful FDA analysis of the completed data set. There is no doubt that the seemingly temporary nature of the refractive effect is an important material fact for a given patient to understand prior to undergoing or considering this procedure.

The refractive procedure likely causes irreversible structural changes to the collagen fibers of the cornea, making the suitability for future refractive procedures unknown. There are no data in the submission regarding retreatments. Appropriate labeling should indeed mention this fact and especially in the light of the substantial refractive drifts seen in the study. In other words, options to later correct a seemingly temporary nature of the

effect are unproven.

Given all the foregoing, if I were advising a patient in a doctor-patient relationship considering this procedure, I would feel obligated to disclose at least the following material facts.

1. There may be up to 32 individual corneal needle sticks placed manually at 90 percent corneal depth.

2. Twenty-five percent of patients have greater than or equal to 1 diopter of induced cylinder at 6 months.

3. A shift in astigmatism axis is more likely than not.

4. Five percent of patients lose greater than or equal to two lines of best corrected visual acuity at 6 months.

5. Patients report increased symptoms of glare, halos, double vision, fluctuation of vision, variation of vision and night driving problems following the procedure.

6. The procedure is unstable with a substantial progressive loss of surgical effect.

7. The current PMA discloses that the duration of the hyperopic drift is unknown.

Assuming that the patient was competent,

had adequate comprehension of the issues and was exercising voluntary choice, I'm hard pressed to say that a reasonably prudent individual would want the particular procedure. Nonetheless, it's the charge of this Panel to determine if the data proffered give a reasonable assurance of safety and efficacy if a patient was indeed interested in this procedure.

This Panel is once again faced with a device that has a seemingly temporary refractive effect. From a prior Panel Meeting, it's the Agency's position that "it's quite reasonable for an Advisory Panel to evaluate a submission which has a nonpermanent use. There are devices that are just temporary. There are a lot of them."

In the past, a marginally effective procedure for hyperopia, the Sunrise LTK procedure, was indeed FDA approved, "for the temporary reduction of hyperopia in 2000."

Given that refractive instability is a major shortcoming of this procedure, the primary indication statement should delineate two crucial material facts.

1. Significant hyperopic shift or loss of surgical effect occurs over the study period.

2. The study fails to prove refractive

stability in the long run, that is the drift may be on-going.

It's important to realize that just as the data do not prove final stability, the data similarly do not prove that the surgical effect completely regresses. That is, the data are insufficient to prove that the effect is either temporary or permanent, albeit we do know that the surgical effect diminishes over the study period and we do know that it does not stop at a defined point in time. Rather than a single word like "temporary", I'd suggest a statement that describes both the loss of surgical effect and the unknown duration of drift such as "refractive stability is unproven for the CK procedure with progressive loss of refractive effect over time."

I'll certainly be interested to hear Panel wordsmithing on this particular issue.

In the PMA's current state, with the major shortcoming of refractive instability, I don't believe that the application is approvable without conditions. Therefore, I'd recommend the following conditions for approval.

1. Complete all enrolled eyes to the 12-month interval with FDA review of all stability analysis and if stability cannot be proven at that

time, hold approval and reanalyze at longer time intervals.

2. Submit all available 24-month data for FDA review prior to considering approval.

3. The study must be completed to 24 months given all the aforementioned issues.

4. Post-market surveillance is mandatory to document if and when the regression stops with appropriate labeling revisions.

5. The labeling should include all relevant material facts.

And rather than listing them I went ahead and put a Panel handout on everybody's table at the end of my slides listing the types of labeling recommendations that I would like to see for consideration.

6. If not already done, eliminate the adjustable energy duration controls as this study was really only tested with .6, .6.

That concludes my initial comments. Thank you so much for your attention.

DR. SUGAR: Thank you. Next, Dr. Weiss?

DR. WEISS: I think my colleagues have very effectively discussed the concerns about this procedure and in the interest of not being repetitive

and in the interest of time I will not repeat their comments, but I'll limit myself to the questions that are before the Panel for discussion.

The first question was are there concerns regarding the incidence of induced cylinder with significant axis shift and its consequent effect on efficacy? I think all the -- Dr. Berman, Dr. Grimmett, Dr. Bradley and myself all have concerns about this. The best corrected visual acuity is only one criteria to evaluate the efficacy and as Dr. Berman has shown us, of the patients who had more than or equal to 1 diopter of astigmatism induced, they had half the rate of achieving 20/20 as those who had less astigmatism induced. So even one line of uncorrected visual acuity difference is very significant when we're dealing with such small amounts of hyperopia.

Nevertheless, I think the way to address this concern is in the patient labeling because there are strict criteria that the FDA has put forward and that the device meets these criteria in terms of the amount of percentages of induction of 2.00 diopters of astigmatism, so this is a patient labeling question that we will sort of hash out.

The second issue is is 12-month follow-up sufficient to provide reasonable assurance of safety

and efficacy and should data for the 21 eyes available at 24 months be required in labeling? We have to apply the FDA criteria for all these questions and in this case we have to admit that the sponsor has met only 2 of the 4 stability criteria at 12 months. Consequently, stability has not been achieved.

This is a very important question for any patient who's going to decide to choose a particular type of refractive procedure and they're entitled to know whether this is a temporary or permanent procedure and we have applied these criteria, namely deciding whether something is temporary or permanent effect to other devices that have come before Panel as was just mentioned the Sunrise laser most recently.

So I think it is incumbent on the FDA and the sponsor to have analysis of the 24-month data to decide at what point, if we can determine, stability is reached and I think this very important to put as well in the labeling that stability has not been reached by 12 months and I would actually prefer to say at 12 months the effect of this device is temporary just so the patient can understand and compare this to other devices that are out there and they are going to be making a selection between.

The third question, does the refractive

correction obtained with this device in light of the rate of change of mean MRSE over time and the incidence of over and under-correction justify the potential risk? And to this I would answer yes. The criteria that the FDA has put forward have been met by the sponsor and the risk of adverse effects are quite low and so I think that the risks are certainly justified.

Question 4, are there concerns regarding the increased incidence of visual symptoms from pre-op levels? Well, here I have a slight concern. The moderate to marked complaints subjectively were a little bit higher than FDA criteria have mandated in the 5 to 7 percent range and I think it's very important to have in the patient booklet a better reflection of exactly what these complaints have changed from pre-op to post-op values. For example, mild complaints of halos, blurred vision, double vision, fluctuation of vision actually doubled between the pre-op visit and the month 6 visit and continued at month 9 and month 12 and it's very important for patients to know not just the percentages, but that these things may be affecting them.

Also, as has been pointed out at the Panel, there appeared to be a slight trend toward

increasing dissatisfaction with time, although statistical parameters were not applied and this follows the effect of regression and decrease in over-correction with time.

Question 5, do the safety and efficacy data presented in the PMA support approval of this device for the requested indication? I would say yes, with the concerns that I've mentioned about the 12 and 24 -- bring the data out to 24 months and deciding whether we are going to call this a temporary effect or when stability is defined.

And as to Question 6, the recommendations for labeling regarding regression of effect, induction of cylinder and incidence of visual symptoms, I would address myself again to the question of stability. I do believe the sponsor is being a little disingenuous by playing around with not being able to see whether this is permanent or temporary and not needing to choose those words, yet at the same time including in the patient labeling a statement saying that LTK reshapes the cornea to temporarily treat hyperopia, as if to make a distinguishing characteristic that LTK is a temporary procedure with this indeed may not. I think you have to basically decide is this temporary of if you don't want to say it's temporary at the 12

months, then bring it out to 24 months and give us a stability time point, but to say that another procedure that a patient may be choosing instead of this is temporary by comparison, I think is a little bit deceptive, just as deceptive as saying you could be treated with a laser versus a warm heat. That has to be described in a little bit better detail as well.

The incidence of the axis shift and the magnitude of induced cylinder as well as the duration that this is occurring for should also be included in the labeling because this could cause significant visual symptoms, even if the best corrected visual acuity is minimally affected and even if there's only a line of uncorrected visual acuity deficit, still I think most of us would not have any problems believing that if a patient has an axis shift of 45 degrees they may have a problem with this.

And in addition, the subjective symptoms the patients should have in the patient booklet, the degree of increase between pre-op and post-op of the symptoms.

DR. SUGAR: Thank you.

DR. ROSENTHAL: Mr. Chairman?

DR. SUGAR: Please.

DR. ROSENTHAL: I think I should say this

now before you start your deliberation that as you all know and I think you've been very good about it, each PMA has to stand on its own and this data has been discussed on its own. There has been reference to other decisions the Panel has made. I think that's reasonable to make a reference to it, but I think no comparison either by you, the Panel or certainly by the company in its labeling will be appropriate. So I think you all are aware of that and I think it's reasonable to point out in historical perspective that the Panel in the past has approved refractive corrections for quote temporary as you have done, but to compare them in any way would be inappropriate.

Thank you.

DR. SUGAR: Thank you. I'd like to suggest a format for proceeding, of going through question by question unless there's objection, and then using that discussion to then come to a motion and discuss motions.

Do you have a comment, Jose?

DR. PULIDO: Yes, since Dr. Rosenthal brought up the historical perspective, we should also realize that the first time that the LTK came up to Panel it was not accepted. It was only after the FDA pushed us to saying that temporary is allowed that the

Panel then allowed the LTK to go through.

DR. ROSENTHAL: I think Dr. Grimmett made that clear. I think he was quoting me.

DR. GRIMMETT: Yes, I was.

DR. SUGAR: Okay. Does anyone object to proceeding question by question?

Then the first question is what are the concerns regarding the incidence of induced cylinder with significant axis shift and its consequent effect on efficacy? And I'd like to have one of the primary reviewers be the first to answer each of these.

Dr. Bradley, do you want to begin?

DR. BRADLEY: Well, I think there has to be concern we have a procedure that is inducing cylinder. We don't know what the root cause of this induction is and clearly those patients with larger amounts of this induced cylinder are not achieving the uncorrected VA that is achievable by those patients who have lower amounts of the induced cylinder. So I think whenever that happens we have to be concerned about it and it certainly is compromising the efficacy. I think as I alluded in my presentation the thing that concerns me is we have no idea where it's coming from and there seems no indication in the near future that it could be improved or remedied.

DR. SUGAR: Thank you. Other comments concerning this issue?

I think that the Agency has a sense of our concern about the induced cylinder. In terms of how specific we need to get beyond what's already been discussed I'm not sure. Can you comment, Ralph?

DR. ROSENTHAL: If the Panel feels they've discussed this sufficiently --

DR. SUGAR: I'm not saying we have. I'm not exactly sure what direction you want us to go.

Bill Mathers?

DR. MATHERS: Yes, Bill Mathers. I'm a little concerned, like my colleagues, that we don't really know why this is occurring and there certainly are several possibilities. I think it could be possible to find out. I think that, for instance, topographic ought to indicate if we have a kind of generalized regular astigmatism or if it's highly irregular and where it is on the cornea and if there's a possibility of improving this or if the procedure is just intrinsically going to do this. And so I don't think the astigmatism is terrible, but I think we don't know why it's occurring. It may be because we're treating in some cases on visual axis, but some of that is closer to the periphery than -- because of

the shape of the cornea. There's lots of questions here that remain unanswered.

It may not preclude us from granting some kind of approval because of its safety and efficacy, but we don't know what's happening.

DR. ROSENTHAL: May I just interject? I think there are certain interesting scientific questions that are always raised by devices and Dr. Mathers has raised them, but whether or not -- I do not feel that it's this Panel's responsibility to try to come to some conclusion as to why there are problems, except if it influences the decision making process and certainly, hopefully, for devices, in general, when they are finally out in the community many of these questions get answered.

DR. SUGAR: In general, the way we answer these is by dumping them into labeling and the suggestion has been made that the labeling includes cylinder induction by degree of induction, loss of acuity related to cylinder induction, instability of cylinder induction and the unpredictability of cylinder axis and I think it's important that if these are put in the labeling that the labeling for the patients not say cylinder axis because that's not meaningful to a patient, but that there be

wordsmithing such that it's understandable to a patient what's being talked about.

Alice?

DR. MATOBA: Also in the labeling we should add that the original study only included patients with astigmatism up to .75 diopters and we don't know whether this effect would be magnified or not in patients with higher levels of astigmatism.

DR. SUGAR: Although my presumption is we're considering approval only in the range that's been studied.

Other comments on cylinder? Does everyone agree that this needs to be addressed in labeling? Any other comments on -- that's Question 1.

No. 2, is 12-month follow-up sufficient to provide reasonable assurance of safety and efficacy? There are 21 eyes available at 20 months. Should data for these eyes be required in the labeling?

It's a two-part question, that is, do we have enough follow-up and (2) what should we do with the data that we have?

Jayne?

DR. WEISS: I think 12-month data is sufficient to assure safety, but I think part of efficacy is whether the effect is stable or not. So

I think I would have questions about efficacy at only 12 months and consequently would like the data from 24 months to be included in the labeling.

DR. SUGAR: Go ahead.

DR. GRIMMETT: Michael Grimmett. As I made in my concluding remarks, with the final interval showing a .48 diopter shift per year whose confidence interval excludes zero and is increasing, I feel that the 12-month data collection should ensue with FDA analysis of that stability to see if it is now decreasing and if the confidence interval includes zero. I would hold approval until that's met.

DR. ROSENTHAL: Excuse me --

DR. SUGAR: You said 12 months. In your presentation you said 12 and then you had another clause about 24-month data.

DR. GRIMMETT: I'd like to see the 24-month data that's available or have the FDA look at it, but I believe the 12-month data should show stability by the current criteria before it's let loose.

DR. SUGAR: So you're suggesting that we get more complete 12-month data?

DR. GRIMMETT: Yes.

DR. SUGAR: And have that re-reviewed --

DR. GRIMMETT: By the FDA. That's correct.

DR. SUGAR: Dr. Huang?

DR. HUANG: I have a real reservation about Mike's final recommendation. So we know this is going to be a temporary procedure would that be reasonable to impose on the post-market surveillance rather than defer the PMA, otherwise, I don't think we will ever get enough data.

DR. SUGAR: Other comments? Dr. McMahon?

DR. McMAHON: Tim McMahon. One of my concerns and maybe one of my questions is with the supposition that this is a transient effect, that if Dr. Bradley's supposition is even remotely correct has somewhere in the neighborhood of a 4-year duration, then there's going to be a tremendous stimuli for retreatment and we have absolutely no idea about this. And I have -- do we have the capacity in the labeling to prevent retreatments in the absence of subsequent study data?

I'm worried that additional treatments will increase irregular astigmatism, reduce the best corrected visual acuity and all the things that have escaped this procedure thus far.

DR. SUGAR: I think in the labeling we can

approve it for the indications and say that this has not been -- we say that there is not data on retreatment. What a physician practicing medicine chooses to do is a different issue that I don't think we can control.

Am I wrong, Ralph?

DR. ROSENTHAL: That's -- you can put, you can certainly put in labeling that there's no data on retreatment. If you have valid scientific justification, you can include in labeling that you do not feel retreatment is warranted, but --

DR. McMAHON: That's like proving the negative.

DR. SUGAR: But it's hard to do in the absence of data either way. But your point, I think is well taken.

DR. ROSENTHAL: Excuse me, Ralph Rosenthal. You can use precautions and warnings to clarify your issue, but to contraindicate retreatment without having any data and any scientific basis of that is very difficult to do.

DR. SUGAR: Jayne?

DR. WEISS: I think we've returned to the issue of temporary versus stable and that's why I think at some point sponsor, as well as FDA has to put

our money down and determine which one this is and that will let us go forward in terms of deciding whether delay approval will go ahead with approval.

I would be of the mind to say to go ahead with approval with the 12-month data that we've been supplied by saying at this point the effects are temporary and we will need the 24-month data to determine stability as opposed to holding up approval waiting for that stability to happen.

DR. SUGAR: I would like to wait until Question 5 in terms of that would be the indication rather than labeling, but the use of the word "temporary" and I assume we'll have a moderately gently heated discussion.

DR. WEISS: I was just addressing that to Mike's comment.

DR. SUGAR: Dr. Huang?

DR. HUANG: Andrew Huang.

DR. SUGAR: And then Dr. Ho.

DR. HUANG: I have a question for the Panelists. I'm still not clear if the Panel's responsibility is to approve the device based on the safety or based on the efficacy.

DR. SUGAR: Both. And to comment on both and we recommend to the Agency, the Agency then

approves or doesn't approve the device.

Dr. Ho?

DR. HO: Allen Ho. My only comment would be that there may not be anything magical about 24-month data and if stability is established prior to that that would be much more comforting to me.

DR. SUGAR: Okay, so last comment on this question.

DR. BRADLEY: It's actually a question.

DR. SUGAR: Dr. Bradley.

DR. BRADLEY: I'm surrounded by such esteemed clinicians and I think the sponsor has already mentioned that treatments for hyperopia tend to have the characteristics we've seen with this particular treatment, that is, initially there's an over-treatment and the patient ends up with myopia. Subsequently, there's a regression and arguably the regression is greater than some of the earlier devices that have been approved.

I'm just wondering what patients do with that? I mean surely we have now a data base of how patients handle this. Are patients opting for some of these other techniques that are out there or are they saying no, I don't want temporary myopia and I'm not going to have a surgery is then going to regress away.

I'm going to lose the effect. Because if that's the case, then I would say perhaps we shouldn't approve this one, but if patients are quite happy with that, then my opinion would change. But I have no knowledge of that.

DR. WEISS: I think our decision should really be made at the Panel just on safety and efficacy requirements and whether or not an individual patient opts for this is a whole separate question which I don't think we really have to address. The company and its stockholders will have to address that one.

DR. SUGAR: Although we can say let the buyer beware and do that in the labeling.

Next is Question 3.

I'm sorry, Bill?

DR. MATHERS: Bill Mathers. We can say that it's effective temporarily at this point because there is some demonstration of efficacy, but we certainly can't say that we know the nature of the permanent correction and we may not at 24 months either.

DR. SUGAR: Again, we'll get to that in the indications and we can also, in addition to these questions, we can recommend post-marketing

surveillance and re-review -- we cannot recommend post-marketing --

DR. ROSENTHAL: Rosenthal. Surveillance, I don't think is the word.

DR. SUGAR: I'm sorry.

DR. ROSENTHAL: You can recommend a post-market evaluation of a cohort.

DR. SUGAR: No. 3. Does the refractive correction obtained with this device in light of the rate of change of mean Manifest Refractive Spherical Equivalent over time and the incidence of over and under-correction justify the potential risks.

Go ahead, Dr. Grimmett?

DR. GRIMMETT: I interpret this question to mean is it reasonably safe despite the limitations of effectiveness. I believe the answer is yes. It's reasonably safe despite the stability questions.

DR. SUGAR: It's sort of worded a little ambiguously. It also says in light of the rate of change of mean Manifest Refractive Spherical Equivalent. So this is really asking, I think, both of us stability and safety.

DR. GRIMMETT: Okay. Well, stability I believe I've made my opinion clear that I don't think the current PMA meets the current FDA definition of

stability and I'm uncomfortable approving unstable procedures that don't meet current FDA definitions, but I do believe that the procedure is reasonably safe.

DR. HUANG: Andrew Huang. I feel that the regression is really biphasic as shown by the graph from the presenters. There's initial over-correction and there's later under-correction and so therefore I think the generalize statement by the sponsors generalizing the statements it is 6 to 10 percent decrease loss of the intended correction, I don't think it's a fair statement. I think the sponsors should clarify the issue and report a natural course of this regression to the consumers.

DR. SUGAR: Again, that's in terms of how we define the indications, because they're suggesting, I think that being the indications and I agree, we can suggest rewording.

Other comments?

Arthur?

DR. BRADLEY: We're trying to assess whether this procedure justifies the potential risk given what we've seen in terms of its effectiveness and it just seems to me that in some ways we're a bit -- we're forced to make this decision prematurely. I

mean the data, as I show, the procedure itself actually increases the variability in the refractive error distribution. I can't imagine how such a procedure can be successful, given in every eye there was a single target end result which is emmetropia. So it seems to indicate there's a huge amount of uncontrolled variability in this procedure which is very worrying to me.

We also know that not only the mean, but a significant proportion of the patients are going to have significant, and I mean clinically significant levels of myopia after the procedure, albeit this is a temporary situation for most of those patients. Again, that worries me in terms of safety, particularly, as I said, these patients have not experienced myopia before. So this is a first time for them.

In the end, I just worry that we have a procedure that has a lot of uncontrolled variability to it. It fails to hit its target in the short term and maybe only hits the target at 9 to 12 months because it so happens the regression is passing through zero at that point. And I just -- I'm looking for evidence to say yes, this is an effective procedure. It actually can render emmetropia is some

reasonable way in a large percentage of the people who are treated and I can't find that. I'm really having trouble with that.

DR. SUGAR: Dr. Mathers?

DR. MATHERS: This is a surgical procedure and all surgical procedures are unstable immediately after the procedure. We take this to a higher standard with a refractive procedure because we're dealing with somebody that can see beforehand, as opposed to say an unstable knee that needs a total knee. But nevertheless, it is a surgical procedure and the fact that it's not perfect immediately after I think it would be to a higher standard to hold that to make it perfect immediately, in general terms.

DR. BRADLEY: Maybe I can respond to that. I think it would be true, if this patient was rushed to the hospital and needed treatment, but that's not the case. I mean these patients have alternative modalities which they can use to correct their farsightedness. So this is an elective procedure and I think we should hold it to a much higher standard. I'm quite comfortable with that higher standard.

DR. SUGAR: Additional comments on Question 3? If not, we'll move on to Question 4. Are there concerns regarding the increased incidence of

visual symptoms from pre-op levels?

We're back to you, Arthur?

DR. BRADLEY: Well, I know we're not allowed to mention other refractive procedures, Ralph, so I'm not going to.

(Laughter.)

But we clearly know this is a ubiquitous result. Any time a refractive surgery is done to the cornea, we have loss of best corrected visual acuity which is, by the way, symptomatic of some optical imperfection. We have increased optical manifestations, also visual manifestations of optical problems: halos, glare around light sources, transient visual, unstable vision, I mean. And it seems like this particular procedure is no different. So it just fits in with the crowd.

DR. SUGAR: Go ahead. Janice?

DR. JURKUS: Janice Jurkus. I have some very serious concerns regarding the changes from when people were pre-op and they said they had no symptoms to post-op and they said that they did have symptoms, even though they may be mild symptoms. I think the person can quite easily tell if they have a symptom or not and I understand that the subjective information that patients given can vary from day to day, but when

you get the amount of change that was noted in the submission that's concerning to me, particularly in terms of the halos around lights and the patients having fluctuating vision and having fluctuating vision in dim illumination because again, the age population that this treatment is for is also the age population that may be developed in cataracts and these can be exacerbated to even a further degree. So that is a very serious concern to me.

DR. SUGAR: Go ahead, Dr. Ho.

DR. HO: Allen Ho. I'm less concerned about those. Any symptomatology that's reported in an uncontrolled fashion and I would say that the bottom line here on satisfaction, 9 out of 10 patients were satisfied.

DR. SUGAR: Okay, other comments? I think Mike and then Jose.

DR. GRIMMETT: That's okay, Jose can go.

DR. PULIDO: Dr. Ho, where was the -- Jose Pulido -- where was the 9 out of 10 satisfaction rate?

DR. HO: Can you guys confirm that?

DR. GRIMMETT: The relative figure was 1 out of 10 were dissatisfied or very dissatisfied and then the satisfaction rate, you'd have to subtract the neutral category out.

DR. HO: Right.

DR. GRIMMETT: So satisfaction may be, if my memory serves me correctly, 70 percent?

DR. PULIDO: Yes, it wasn't 9 out of 10.

DR. GRIMMETT: But you'd have to look at the tables.

DR. HO: Okay, Allen Ho. I'm corrected, but the point is you have to be very careful about looking at rates of symptoms in the context of an uncontrolled setting.

DR. GRIMMETT: Mike Grimmett again. I think -- I agree with Dr. Jurkus' concern over the symptom data and I think those issues can be dealt with in the labeling as given an example of a nice table that Dr. Berman presented on the very next slide, Slide 15, as well as delineating the percent of patients that had no symptoms pre-op, versus no symptoms post-op. That was the type of data I presented in my presentation. I just reversed the numbers to yes rather than no, but I think both ways of presenting the data would be appropriate in the labeling.

DR. SUGAR: I'd like to move on then to Question 5. Do the safety and efficacy data presented in this PMA support approval of this device for the

requested indication? That's getting back to the wordsmithing we were talking about. Is the requested indication appropriate as worded, based on the study outcome?

And then the last page of the sponsor's presentation, I think, had their recommended wording if I'm correct.

This is CK treatment for the indication of spherical hyperopia in the range of +0.75 to +3.25 diopter for cycloplegic spherical hyperopia, -0.75 diopters or less of refractive astigmatism, +0.75 to +3.00 diopters of cycloplegic spherical equivalent. In patients with less than .50 diopter difference between pre-operative manifest and cycloplegic refractions who are over 40 years of age, that's the up front indication in terms of patient refractive error and age.

The magnitude of correction diminishes over time with an average loss of approximately 6 percent by paired analysis manifest refractive spherical equivalent of the intended correction at 1 year. The proportion of intended correction retained beyond 12 months is undetermined.

I guess I'd like to deal with first the two main bullets, the dioptric correction for sphere

and cylinder and the difference between pre-manifest and cycloplegic refractions in patients 40 years of age or older.

Are there comments suggesting to modify those. Please, Jayne?

DR. WEISS: Well, I would agree with the three bullets as listed, except would want to -- if the device was going to be approved today, I would like to add CK treatment for the temporary reduction and just add the word temporary which can be changed if the 24-month data which will be reviewed by the FDA shows stability at that point.

DR. SUGAR: Okay, I sort of tried to separate these so that we can -- I'm not trying to avoid anything, but -- in a way I am, but that's different.

The last two bullets are really discussing that wording and it could be put up front or at the end that I think ultimately FDA will decide.

DR. WEISS: Jayne Weiss again. The erst of the bullets as listed that you're referring to I would agree with.

DR. SUGAR: Dr. Huang.

DR. HUANG: Andrew Huang. I have a little bit reservation about the proposed three indications.

I think the data presented by the reviewers are stratified patients of pre-operative hyperopia, so you can see there's a drastic difference between the efficacy between the +2.00 of greater or the +2.00 or lower hyperopia. So I think maybe we can review the data if the sponsor can stratify the information according to the pre-operative information and then show the efficacy is indeed much better in one group and then we probably can narrow the indication of +.75 to +2.00 or +2.50 instead of all the way to +3.25 to increase the safety margin.

DR. SUGAR: Okay, there are two different ways that we've dealt with this. One is to change the indication. The other is to leave the indication, but include in the labeling and physician information require that it be in -- that information that there be stratification and demonstration of efficacy and that the patient be told that there are different efficacious at different rates. I think Mike and then Alice.

DR. GRIMMETT: Mike Grimmett. I would favor the latter option that Dr. Sugar discussed of dealing with it in the labeling. We all know that most of the refractive procedures have decreasing efficacy as the level of emmetropia increases. I

don't think it would be exactly fair or right to chop it off at the higher range unless there was such a paucity of data at the higher range that it wouldn't warrant the approval.

I would leave the first three bullet points alone and deal with the decreasing efficacy in the labeling.

DR. SUGAR: Dr. Matoba?

DR. MATOBA: Dr. Alice Matoba. I agree with Dr. Grimmett. I think the patients who had the higher levels of pre-operative hyperopia were more satisfied and happier with the procedure.

DR. HUANG: But have less effect.

DR. SUGAR: That's correct. Bill?

DR. MATHERS: Bill Mathers. But that is the group actually that needs -- that is most interested in having the procedure, so I think that whereas the efficacy, the effect may not be quite as great, it would be unfortunate to remove that group from this.

DR. SUGAR: Okay, I'd now like to deal with the indication, the wording in the indication for our concern about stability or loss of effect. The sponsor suggests the magnitude of correction diminishes over time with an average loss of

approximately 6 percent of the intended correction at 1 year.

DR. BRADLEY: I'm a bit worried by this because if we replace one year, perhaps 11 months and 3 days it would be zero percent because there is some point at which that function crosses zero and it may just be fortuitous that the cross over one is close to 1 year and what is misleading about that is the implication that boy, it's right on target and there is no indication that, in fact, that was a moving target. So I'm a bit worried about an incorrect implication of that statement.

DR. SUGAR: Please, Dr. Grimmett?

DR. GRIMMETT: I agree with Dr. Bradley's concerns. I think the comparison to intended correction with the moving target is misleading to consumers. The way that I looked at it or analyzed it, at pre-op, these patients had a mean hyperopia of 1.86 and at month 1 they were corrected to a mean of -.56 diopters for a mean total of 2.42 diopters of surgical effect at the 1 month visit. They lost .8. That's about a third of the effect was being lost with time, so in my presentation when I said they lost about a third of the surgical effect, that's the way I was looking at it and I feel the 6 percent figure

would give misleading reassurance to consumers. I'm not in favor of the comparisons to intended correction because it is a moving target.

DR. SUGAR: Bill?

DR. MATHERS: Bill Mathers. I think it would be more accurate at the present time for the public to understand that it's at about a .50 diopter per year in -- but this is only an estimate. Because they care what happens in the immediate time, but really in terms of what they can look forward to once things settle out, it looks like it's going to be somewhere on .50 a diopter a year. And that's perhaps a closer understanding to -- although we don't know this.

DR. SUGAR: Jayne?

DR. WEISS: I would like to put this in terms that anyone could understand and I think without looking at the numbers, basically at one year, this is not stable. The effect is not stabilized at one year. I'm not sure that all patients would understand the significance of the .50 diopter versus 1.00 diopter whereas if you say it's not stable, well, it's not stable.

DR. SUGAR: So you're suggesting?

DR. WEISS: Well, I would still -- I don't

know if I dare to go back to the first line and put in "temporary", but I won't say that, but I thought it. But I would agree with the other two reviewers, the last two statements by the sponsor sort of sanitize and minimize what our concern is that at one year time stability of the refractive effect has not been achieved for the consumer advocate might wordsmith a better way to put this for consumers, but that's basically what I'd like to convey.

DR. SUGAR: Rich McCarley?

MR. McCARLEY: Just a comment. I mean I don't know if we're actually trying to wordsmith it here, but it seems like three comments can solve, I think, at least in my mind, you know, the results may diminish over time or the stability has not been established over time. Average loss at one year is 6 percent. Long term stability has not yet been established. I mean essentially you're telling them what the truth is. The long-term stability hasn't been established. What we do know at least with the data we have is that at one year it appears to be 6 percent and up front you tell them it may diminish over time. You don't know -- I'm not sure whether the statement that they have even presented is correct because it says that there's an average or a mean loss

of 6 -- a regression of 6 percent, but did all patients regress? So I think it's simply being up front and telling them the results may diminish over time, the average loss at one year was 6 percent and the long-term stability has not yet been determined.

DR. SUGAR: My recommendation would be that if we have a statement similar to where there is significant likelihood of regression of effect over at least 1-year period, over at least a 1-year period of time, which may be too nebulous, but I don't think -- I think that 6 percent is too specific and misleading.

Bill?

DR. MATHERS: Yes. I would agree with you. If you're going to say something, you can't say the 6 percent. I think that that's too soft. You either need to be more nebulous or you make it a little more accurate, according to what we currently think.

DR. SUGAR: Too gentle. Tim?

DR. McMAHON: Two things. I'd actually like to put in Dr. Weiss' comment on the first line that we do put in the point of the temporary reduction of spherical hyperopia and then to address the bullet point with regard to the 6 percent. I think you can accomplish that by actually posting what the ranges

are for both change from maximum correction as Dr. Grimmett was discussing as well as from intended correction and if you show the breadth of the range, then both physician and patient will have some idea of what that spread is.

DR. SUGAR: Jose?

DR. PULIDO: Going back this morning, Joel, you asked me why I brought up that case of the patient with that adverse event. It was a patient that had a -2.00. Dr. Bradley later talked about the -2.00 situation as well and my concern and it's been brought up by the Panel reviewers is the unpredictability and nowhere in this yet have we discussed the fact that it's not a very predictable procedure. Do we need to put that somewhere in the labeling?

DR. SUGAR: I think that there will be agreement to that. Right now, I think we're still dealing with the indications, but I agree with you wholeheartedly.

Arthur? I guess I'm not supposed to agree. I'm supposed to be neutral.

MS. THORNTON: You can agree.

DR. SUGAR: I can? Thank you.

DR. BRADLEY: I'll try to preface the

agreement with -- I'll try to agree with Joel and with Jose here. This is Arthur Bradley. Yeah, I think that second from last bullet is unique, really, compared to the other ones and one wonders if it's appropriate in the indications for use. Because really it's sort of an apology for a statement of the inaccuracy of the procedure. And it's only one of the inaccuracies is as I spoke before, the procedure itself has a lot of variability, so inherent inaccuracy and this is just mentioning one summary statistic of a whole variety of errors produced by this procedure and I think if in the indications it's appropriate to put a summary of the inaccuracies of the procedure, I think that would be fair enough, but this is completely inappropriate as such a summary, but I'm not sure that that would be an appropriate thing to put in the indications, but it seems to me that's what it is. It's a statement of the inaccuracy of the procedure and I think there are a variety of things we'd like to put in such a summary statement.

DR. SUGAR: Jose?

DR. PULIDO: So, Joel, you castigated me for putting, for talking about the unpredictability --

DR. SUGAR: I enjoyed it.

(Laughter.)

DR. PULIDO: But really, I think it should say something to the effect of CK treatment for the unpredictable and temporary reduction of spherical hyperopia in the range of dah, dah, dah.

DR. SUGAR: No comment. Jayne?

DR. WEISS: I know we're not supposed to speak about other lasers or other procedures, but I do think we have to apply standard criteria to the devices that we evaluate here and I think putting that in would hold it to a higher level than we've been applying to any other device. I think the indications are meant for what you use it for and the sponsor has indicated that. We're discussing how we can indicate in a clearer fashion that there's not stability at one year, but to talk about the variability, I think that should be put into the labeling as opposed into the indications because that's the way we usually do it.

DR. SUGAR: Mike and then Bill.

DR. GRIMMETT: Mike Grimmett. I'm not in favor of a single word temporary or permanent. I just don't think that the data are sufficient to prove it one way or the other. We simply don't know.

What we do know is that the refractive effect diminishes over the study period and we don't know where it stops, so I would with those two points

I would somehow like them in a sentence and I suggested one, but there's numerous ways to do it to communicate those two particular points. I'm not a fan of the word temporary.

DR. SUGAR: Can you restate yours?

DR. GRIMMETT: Sure. My was "refractive stability is unproven for the CK procedure, with progressive loss of refractive effective over time." I'm certain that can be wordsmithed to something better.

DR. SUGAR: That's worded more as a labeling thing rather than as an indication thing, unless you add CK treatment for the reduction of spherical hyperopia, where --

DR. WEISS: This is just a question to yourself or Dr. Rosenthal. In terms of the devices that we look at ordinarily, ordinarily does it have permanent versus temporary in the wording?

DR. ROSENTHAL: This is Rosenthal. No. It says for the -- I forget what the exact word is -- for the correction of, which implies for the correction of. And for the temporary correction of implies for the temporary correction of.

DR. WEISS: So this is -- Jayne Weiss again. This is where my concern lies is by not

putting the word "temporary" are we implying "permanent"? And that's why I'm going back to past experience with other devices, just so that the consumer can have a uniform way of comparing things?

DR. SUGAR: My sense of the committee is that we all agree that there needs to be some modifier that says -- that based on the information we have now it does not appear to be stable and how we say that is what we're discussing. I agree.

Bill, I think, was next.

DR. MATHERS: Well, it was a couple of comments ago, but I think that all of our assessment of both the stability and the accuracy is based on a relative effect and that we -- although we don't talk about other systems, I mean none of this is accurate to the point at which we -- and to the level that we can measure. They're all inaccurate and this is inaccurate as well, but in my opinion it isn't so wildly inaccurate that we should particularly characterize it as being an inaccurate approach.

But I do think it is important to address, to not let it stand either through labeling or through this indication use, that it is intended to be permanent because other systems of this are permanent, so this is a little different and somehow we ought to

indicate that.

DR. SUGAR: How would you suggest that we indicate that in the indications?

DR. MATHERS: Well, if we put temporary in here now or if we recommend that -- and we learn later that it is different would it be removed? Because -- I mean we don't have a complete data set here.

DR. SUGAR: It could be.

DR. ROSENTHAL: Rosenthal. Dr. Mathers, yes. The company could come back with 2-year or 18-month or 3-year or 6-year and ask for the elimination of the word or change in the indication based upon the data.

DR. MATHERS: Because if I'm being intellectually honest about how this is now, it is the temporary effect in my mind now.

DR. SUGAR: Go ahead, Alice.

DR. MATOBA: Alice Matoba. I think permanent is actually a relative term when you're speaking about these sorts of procedures and my question is are these last two bullets really indications? Shouldn't they actually belong in another part? Isn't it really more like a warning or a labeling? Couldn't we just approve the first three bullets and then move on?

DR. SUGAR: I think that the last two bullets modify the first bullet and certainly that information, this is opinion, should be in the labeling.

DR. MATOBA: Okay.

DR. SUGAR: The question is whether we approve this for treatment for the reduction -- approve this treatment for the reduction of spherical hyperopia or we approve this treatment for temporary or permanent, whatever.

DR. MATOBA: Okay, my opinion is that the last two bullets are not indications and they're just modifications.

DR. SUGAR: I personally -- I said this when we reviewed another hyperopia correction. I think temporary implies that it is never permanent and I think temporary is an inadequate word to describe what we're trying to say, but I don't know what the right word is and I made a suggestion and I think there have been other suggestions.

Is anyone willing to take the bull by the horns, as it were?

Bill?

DR. MATHERS: If you left the initial bullet to say "for the reduction" and you left the

second to the last bullet to say "the magnitude of the correction is temporary" down there, it would still do the same thing, although I do agree both those are --

DR. SUGAR: Does "diminishes over time" say temporary sufficiently for you or not?

DR. MATHERS: I think it should say temporary.

DR. SUGAR: Jayne?

DR. WEISS: I understand Dr. Matoba's confusion with the last two statements because I think it's a way of skirting the issue of whether it's temporary or not. And I think they sort of imply it's temporary, but don't say it's temporary and I think it would just be easier to call it for what it is. At the present point it's temporary and if we have a 24-month data, if the FDA is now reviewing that and they see that indeed it stabilizes at 18 months, then that can be easily taken out even before it's on the market. But if the sponsor is going to come forward to us with incomplete data, then we can only act on what we see and I think it is temporary at 12 months.

DR. SUGAR: Bill?

DR. MATHERS: I guess that I kind of agree with you that temporary is a little bit too harsh a statement and if we just said the magnitude of the

correction diminishes over time period, then we are vague, but we are conveying that as a statement and you don't really have to say it's temporary because temporary really means it's never permanent. I agree with you about that.

DR. MATOBA: We don't know that.

DR. MATHERS: No, we don't know that.

DR. MATOBA: It could go down for another year and then just -- Alice Matoba. We don't know that it's temporary. It could keep going -- the effect could go down for another year and then stabilize completely.

DR. WEISS: That's only because we've been forced to meet here without the complete data set.

DR. MATHERS: Correct.

DR. WEISS: That's why we don't know it and the data set is out there, so someone knows it.

DR. MATOBA: Alice Matoba, so I think we can say neither temporary nor permanent.

DR. WEISS: That's my --

DR. SUGAR: Joel? Tim?

DR. McMAHON: I disagree with that. We're faced with a set of data that we're supposed to comment on and it doesn't show stability on that basis. The description is more temporary than

anything else. Now whether it's going to be like years down the line is something we can speculate on, but we're being asked to advise on and it is not stable and the effect is going away.

DR. SUGAR: Dr. Ho?

DR. HO: Allen Ho. I just wanted to make a specific suggestion to include the first three bullets as indication and then the last two bullets, I would be personally comfortable with, "the magnitude of correction diminishes over time." And then the last bullet stands as is.

DR. SUGAR: Jose?

DR. PULIDO: Well, Jose Pulido. Treatment for the unstable reduction of spherical hyperopia.

DR. SUGAR: I wonder if it's appropriate or not to mention in another review this committee looked at a suggested indication where the magnitude of correction diminishes over time, where it said treatment for the reduction of hyperopia where the magnitude of correction diminishes over time and we changed that to temporary. Yeah, I personally favor where the magnitude of correction diminishes over time, but putting it up in the first sentence.

I suspect we've given you a sense of where we are. We haven't? Okay.

DR. ROSENTHAL: Dr. Rosenthal. You've given us a sense. You're going to have to vote. The sense of the Panel has been clarified, but you're going to have to ultimately vote.

DR. SUGAR: I understand. We're still discussing.

DR. BRADLEY: The suggestion of Dr. Ho that we simply just include the very first part of that second from last bullet, the magnitude of correction diminishes over time period seems to me a way which accurately describes the result. It doesn't put any potentially misleading statistic in there like 6 percent and we don't have to call it temporary. We don't have to call it permanent. We don't have to get embroiled in any of that. We're just stating a very simple fact. The fact is the magnitude of the correction diminishes over time. And then the next bullet comes along basically saying well, we don't know what's going to happen beyond 12 months which is correct. So --

DR. SUGAR: Although it's been suggested that that be taken out of the indications, that last bullet and be put in the labeling.

DR. BRADLEY: I don't think either of them are indications, but we're discussing them as

indications. I personally think they should be dropped completely and put in the labeling. But if we want something like this in the indications, I think what Dr. Ho suggested is a very good suggestion.

DR. SUGAR: Dr. Weiss?

DR. WEISS: Jayne Weiss. The concern or the issue that you just brought up is the concern that I have that we're applying for similar phenomena to different companies, different wording and some of them may be much more favorable and some of them are less favorable and for a patient who is comparing two potential procedures they can have, I would think it would be clearer for the consumer to have similar wording to convey similar issues. And that is where my concern is as we recently looked at another device whose name won't get mentioned because I'm not discussing other devices, but we dealt with the issue of stability and because it was not stable at the time point that was given to us, we said it was temporary. Now of course, no one knows that's going to be in 50 years or 20 years. You can get ridiculous as far as final time points. Yes, at some point -- but all the Panel can do is look at the data we have. So if we have data at 12 months and it's not stable at 12 months, then why should we be giving different sets of

wording for the same phenomena to different companies?

DR. HUANG: Andrew Huang. In addition to the wording, I think that that's a fair statement, but I think the indication we should look into the substance of the indication. If we think that two or three similar devices provide similar effect, then if we provide a different range of the allowable correction, then that will be a disfavor to one of the companies.

DR. SUGAR: Could you clarify?

DR. HUANG: Well, I'm not sure about an indication of other companies, but obviously --

DR. SUGAR: That's not relevant to this.

DR. HUANG: That's what I'm saying, but the whole point is if we take into Dr. Weiss' discussion into consideration that we have to give the fair wording to the indication, labeling for this company, then we should also take into the other factors into consideration in terms of --

DR. SUGAR: I think we should be fair based on the data that's presented to us and what Ralph is going to say is not relative to another product.

DR. HUANG: That brings to mind another point on Dr. Grimmett's Slide 22 and obviously the

amount of under-correction greater than 1.00 diopter is significantly more in the patient in the pre-operative hyperopia of greater than 2.25 diopters. The difference is 5 or 6 orders of magnitude, so I think that narrowing of the indication probably, should be discussed.

DR. SUGAR: Actually, we did discuss that earlier and at least the --

DR. HUANG: I know I may be in the minority.

DR. SUGAR: No, but that should certainly be in the labeling. But I think we also -- we're going to go back and vote on these one by one.

Janice was next.

DR. JURKUS: I just wanted to say that I agree with Dr. Weiss. I think it should be stated right up front that this is a temporary reduction. We don't know if it's permanent. And if you don't put that in it would appear to the consumer and the person buying this device that it would be permanent. And it can be removed if it needs to be removed at a later time. I think it's quite important that it's put right in the very front.

DR. SUGAR: Okay, the sixth -- I'm taking the prerogative of moving on to the sixth question.

What are your recommendations regarding regression of effect, induction of cylinder and incidence of visual symptoms? Are there any additional labeling recommendations?

And I'd like to ask Mike to go through this since he listed them I think in his presentation.

DR. GRIMMETT: Sure. Mike Grimmett. On the last page of the copy of the slide handouts I listed suggested labeling considerations. Everyone should have it in front of them. We've already discussed 3, 4 and 5. Joel Sugar mentioned about the induction of cylinder data.

These pretty much speak for themselves. Number 1, include the spectrum of best corrected visual acuity loss at each exam interval and state that of those 24 patients losing best corrected vision at 6 months or beyond, half of those patients are dissatisfied.

No. 2, include the subjective symptom data. I would suggest to include a slide like Dr. Berman suggested in Slide 15. And also include those patients who had no symptoms pre-op versus no symptoms post-op.

No. 6, include predictability data. I don't think there's any argument there.

No. 7, I would include a statement regarding Dr. Bradley and my concern regarding the predictability that the post-operative standard deviations of the mean refraction actually increase after this procedure.

No. 8, is getting to Dr. Huang's concern of including a statement of decreasing efficacy as a pre-op hyperopia increases supported by several features: (a) uncorrected visual acuity data showing lower rates of 20/20 or better for higher hyperopes. (2) the proportion of undercorrection is greater than 1.00 diopter is increased in the higher hyperopic group and (3) the proportion of eyes achieving plus or minus .50 or plus or minus 1.00 of intended decreases as the range of hyperopia increases.

No. 9 was regarding the instability and I listed the five or six features I listed in my slide that we've discussed at length already.

No. 10 was an additional issue regarding the reduction in spectacle or contact lens dependence. I put that in before I knew that -- I think Dr. Weiss asked that was the pre-op spectacle dependence known and since it's not known, I guess I retract No. 10. I don't think you can make a comparison when it's not known pre-op.

DR. SUGAR: If you take out the word "reduction" you can still ask for the data if they have it.

DR. GRIMMETT: Yes, they know what the data is post-op. They include it in Amendment 11. I think it's a useful piece of information. I just now don't know what to compare it to.

11 was regarding satisfaction data as has been mentioned regarding a 1 in 10 rate of dissatisfaction.

No. 12 is the manufacturer has already suggested to include a statement regarding a lack of retreatment data and therefore the suitability for future refractive procedures is unknown. I think that's a crucial issue because of the decline in refractive effect with time. It's critical that the patient know that future retreatments, it's really unknown what effect you're going to get.

No. 13, we just talked about the indications for statement, so 13 we've already discussed.

DR. SUGAR: In there, there's not a statement about data beyond 12 months or whatever data is presented is not available at the present time, right? Should that be in the labeling?

I don't know if there will be data put in including 24 months, but should there be a statement that data beyond a certain time period is not yet available?

DR. GRIMMETT: Oh sure. I would agree with that.

DR. ROSENTHAL: Mr. Chairman, Rosenthal. Certainly, the Panel, if they feel data beyond 12 months is required to be put in the labeling, you can request that be done or you can do it in a post-market arena where the labeling can then be altered afterwards.

DR. SUGAR: Or we can do both.

DR. ROSENTHAL: You can do both or you can do neither.

DR. SUGAR: I'm sort of suggesting we do both.

Jose?

DR. PULIDO: Jose Pulido. I would also like to include what we talked about this morning, any implant of electrical devices in patients would be a contraindication for use in those cases.

I would like to ask the Panel their feeling about patients that have pre-existing narrow angles. They were not included in the study. Should

there be something in the warnings and precautions about those patients?

DR. SUGAR: Again, in the absence of data, it's worth at least stating that the effect on narrow angles is not yet known.

DR. PULIDO: And also, I would like to know from the Panel what they feel about the part where it says onset of cataracts unrelated to age, systemic disease or trauma as a potential adverse effect of the device. I guess they're alluding to the fact that this is microwave energy and microwaves can cause cataracts.

We don't know -- this was --

DR. ROSENTHAL: This is not microwave. This is radio frequency.

DR. PULIDO: It's not microwave? Okay. So radio frequency, do we know the effects of these radio frequencies on cataracts?

DR. SUGAR: Why doesn't the sponsor come to the table and answer so we can get it on the record.

You were reading from their proposed contraindications or proposed --

DR. PULIDO: Yes, correct.

DR. SUGAR: This is just to answer a

specific question. You'll get your --

DR. DURRIE: I think we're all familiar as ophthalmic surgeons to electro cautery that we use, bipolar cautery which is the same radio frequency waves and there's nothing I know of that has caused cataracts with the bipolar uses of cautery in the operating room.

So this i snot microwave. It's radio frequency, like bipolar cautery.

DR. SUGAR: Dr. Ho?

DR. HO: I'm just trying to puzzle through what I think is an important point. In Michael Grimmett's statement regarding reduction in spectacle or contact lens usage. I think that's a very important point for a consumer to try and appreciate. On the other hand, I think we're a little tight because we don't have the data from what the pre-procedure usage was. Can the sponsors comment to at least give me a sense for what the post-procedure dependence upon other correction was?

DR. SUGAR: While they're coming up, I can make a comment that we have in other labelings asked them to supply data of what, how many proportion of patients still use spectacles after the procedure.

DR. HO: It's a figure that will just hang

out there in my mind as someone who is a trialist, but it's clearly and I'm a retina surgeon so I don't talk to patients too much about this, but that is clearly the driving force behind people even beginning to consider their options for refractive surgery. It's a lessened dependence upon encumbering devices.

DR. SUGAR: So you're supporting there being that data?

DR. HO: I'd like to hear what the data is first.

DR. McDONALD: Marguerite McDonald. Fourteen percent of patients reported using distance spectacle correction at 6 months and at no time point at 3 months or later did more than 20 percent of patients use spectacle correction for distance.

DR. SUGAR: So you're suggesting that there be some statement including that information?

DR. HO: I'd like to puzzle through it with the committee, because I think in terms of language for labeling that is a very important point. Perhaps something that will hang in a patient's mind more so than cylinder shifts and diopter shifts, etcetera. So I'd like to hear other comments.

DR. SUGAR: Jayne?

DR. WEISS: Jayne Weiss, is there any way

for the sponsor subsequently to get that information, how many patients had pre-op contacts or distance glasses?

DR. SUGAR: Dan?

DR. DURRIE: I think we need to remember, I think 100 percent of these people wore glasses pre-op. I mean that's why they came in. On all of the patients I know of, we didn't ask that in the questionnaires, but these patients came in not because they were doing well and didn't need glasses. They all came in and had this procedure because they were wearing glasses and having problems with it. This was a distance only study, so this wasn't done to get rid of the reading glasses. So these were 53-year-old hyperopes who were having problems, that's why they came in. So I would say that 90 percent plus of them were wearing glasses pre-op for distance or they wouldn't have even thought about having this procedure.

DR. SUGAR: Did you have an additional comment?

DR. WEISS: I would assume there would be a certain number of the +.75s or the +1.00s or the +1.25s for vanity's sake, whatever, that might have been walking about blurred, so we would need the data

if we're going to put it in there, the actual numbers.

DR. HO: In Philadelphia, some of the +3.00s walk around. They just can't see and they'd be very happy with this surgery, no matter what. But seriously, I think that number is a very important number and Dr. Durrie's comments stand to reason, it would be more comfortable having that, perhaps making a disclaimer about not knowing exactly the number of patients that had used glasses for distance preoperatively would be fair and accurate and saying this is the results that we have after the procedure.

DR. SUGAR: I personally think it doesn't matter what it was before. What matters to the patients is what is after, but the sense of it is that we want information on -- and/or contact lens dependence following the procedure.

Jayne?

DR. WEISS: Jayne Weiss. I would like something in the labeling for the patients to sort of convey that initially they may expect an over-correction and some myopia and that there is a gradual drop off and not to expect the semi-final result until 6 to 9 months so that patients understand this is going to be a long process.

DR. SUGAR: Okay. The sirens are not

coming for us yet, I don't think. I think we have dealt with adequately or inadequately all six questions. Are there additional issues that the Panel would like to raise? The process would be then to have open public hearing: FDA posing statements, sponsor posing statements and then we'll go through the formal proposal, formal motion and discussion and voting options.

Tim?

DR. McMAHON: Tim McMahon. I didn't see this raised and if I missed it, I apologize, but there's been nothing mentioned about the immediate post-operative pain levels, duration and management issues. I was wondering if any of the investigators or the sponsor wants to comment on that?

DR. SUGAR: Dr. McDonald?

DR. McDONALD: Marguerite McDonald. The immediate post-op discomfort is minimal. People either report no sensation whatsoever or a mild foreign body sensation for 2 to 4 hours. Most report taking no pain killers or maybe a Tylenol, so it's very minimal.

DR. McMAHON: Thank you.

DR. SUGAR: Dr. Bradley?

DR. BRADLEY: Just to remind us of

something, I and a couple of other people mentioned earlier, I think it's important for the patients to have a good indication of what the actual procedure is and describing it as gently heating your cornea really is an inadequate description. It might work for marketing, but it's not adequate for FDA patient information.

DR. SUGAR: So that's suggesting changing the wording in the patient information booklet.

Okay. Hearing no additional discussion, I'm sorry, I hear additional discussion.

DR. MATHERS: You might say controlled heating rather than gentle. Because on a relative scale it is controlled.

DR. BRADLEY: I think if I hold a match to my cornea it's fairly well controlled, but --

(Laughter.)

I'm not sure I want to admit to that last comment.

DR. SUGAR: Okay, we'll now move on to the open public hearing session. Is there anyone from the public that would like to make a comment, a relevant comment?

(Pause.)

Hearing no such interest, the FDA now has

five minutes for its closing comments and I will hold them to that five minutes.

DR. ROSENTHAL: I'd like to thank the Panel for an excellent discussion of the issues and am particularly to the primary reviewers for very thoughtful reviews.

DR. SUGAR: Would the sponsor like to comment?

DR. GORDON: Judy Gordon. We, too, would like to thank the Panel and FDA for some very good comments and I think we'll endeavor to communicate the gist of everything that's been discussed here as best we can in an articulate fashion in the labeling and particularly in the patient information brochure so that we convey the information accurately. So thank you again for your input.

DR. SUGAR: Next, Sally Thornton will read our voting options.

MS. THORNTON: These are the options for the Panel recommendation on this pre-market approval application.

The medical device amendments to the Federal Food, Drug, and Cosmetic Act is amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an

expert advisory panel on designated medical device pre-market approval applications or PMAs that are filed with the Agency.

The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probably benefits to health, under conditions on intended use outweigh any probable risk.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows:

Approval, if there are no conditions attached.

Approvable with condition. The Panel may recommend that the PMA be found approvable subject to specified conditions such as physician or patient education, labeling changes or further analysis of existing data. Prior to voting all of the conditions

should be discussed by the Panel.

Not approvable. The Panel may recommend that the PMA is not approval if the data do not provide a reasonable assurance that this device is safe or if a reasonable assurance has not been given that the device is effective, under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Following the voting, the Chair will ask each Panel Member to present a brief statement outlining the reasons for their vote.

DR. SUGAR: Thank you. I would like to ask for a motion to be made from the floor concerning this PMA.

DR. GRIMMETT: Mike Grimmett. I'd like to make a motion that the Refractec PMA is approval with conditions. I assume we're going to talk about the indications statement separately. Is that right? Vote on it separately?

DR. SUGAR: No. I think your motion should be -- the --

DR. GRIMMETT: Let's leave it at approvable with conditions and we will discuss each condition and vote on them separately.

DR. SUGAR: That's fine.

MS. THORNTON: Each one has to be discussed and voted on separately.

DR. SUGAR: But it could be also approval for the following indication and then with conditions.

A motion has been made. Is there a second to the motion?

[Motion was seconded.]

DR. SUGAR: Then we vote on this motion? No.

MS. THORNTON: You go through each condition, vote on each condition.

DR. SUGAR: This is where I need help.

MS. THORNTON: That's okay.

DR. SUGAR: So a motion has been made and seconded that this be approvable with conditions. We'd like to now flesh out the conditions, and I'd like to first ask that the indications be stated.

Jane would like to do that.

DR. WEISS: Jayne Weiss. I would propose that the indications for the procedure be listed as follows: CK treatment for the temporary reduction of spherical hyperopia in the range of +.75 to +3.25 diopters of cycloplegic spherical hyperopia, -0.75 diopters or less of refractive astigmatism, +0.75 to +3.00 diopters of cycloplegic spherical equivalent.

And would you like me to continue through this whole sheet or do you want to go through each thing and vote on it separately?

DR. SUGAR: I'd like to, if you could state the indications and then we can vote on that as a single unit.

DR. WEISS: Second point being in patients with less than or equal to 0.5 diopters difference between preoperative manifest and cycloplegic refractions in patients 40 years of age or older, refractive stability is unproven for the CK procedure. The proportion of intended correction retained beyond 12 months is undetermined.

DR. SUGAR: Is there a second to that? Is there a different motion?

DR. McMAHON: Jayne, would you accept an amendment to incorporate Dr. Ho's comment about that one bullet, about the magnitude of correction which read as "the magnitude of correction diminishes over time."

DR. SUGAR: The period meaning that the last two clauses that Jayne had would not be in the statement?

DR. McMAHON: The last part of the second to the last bullet would not be, but the very last